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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,327	09/03/1999	SARAH ANNE ROBERTSON	A20-005	2475

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/380,327	Applicant(s) ROBERTSON ET AL.	
	Examiner Michail A. Belyavskyi	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *105-114; 116-119, 121-122, 124-127,132-134 and 141-144*.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached .
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

S.C.O

1. Claims 105-112, 116-119, 121-122, 124-125, 127, 132, 134 and 141-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 in view of Lea et al (Am J Reprod Immunol (34(1)), Nocera cf al (.Am J. Reprod. Immunology 33: 282-291, 1995) ; Clark et al (Hum Reprod 9(12): 2270-7, Dec 1994,), Thomas et al., (Am J Reprod. Immunol 644): 185-9, Dec 1984;), Thaler et al (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989;) and Prakash et a., l (Reproductive Immunology 70: 403-412, 1981) in view of the known fact disclosed in the Specification on overlapping pages 10-11 for the same reasons set forth in the previous Office Action, mailed on 06/20/05 and 03/24/05 .

Applicant's arguments, filed 06/24/05 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) US Patent '825 does not suggest a method of treating recurrent miscarriage by inducing specific immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance; ii) dosages and dose regimen of the TGF b administration of the instant claims are distinct from US Patent '825 (iii) none of the secondary references teach or suggest a method of treating infertility by the induction of immune tolerance by exposing a mucosal surface of the prospective mother to semen or MHC class I antigen;

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

As was stated in the previous Office Actions , US Patent ' 825 teaches a method of treating infertility by administering TGFP, such as TGF/I, TGFIQ, TGF/3, and TGFIW (See column 5, line 9-1 1, in particular) along with antigens such as sperm into the reproductive track (genital mucosal surface) of the a female to bolster the chances that a pregnancy will be sustained by increasing the success rate of implantation (See column 5 line 9-12, claim 4 of US Patent' 825 patent, in particular). The reference TGFb may be administered either before, after or simultaneously with the male antigens such sperms of the prospective father which are known to express MHC class I molecule on the surface (sperm antigens) and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5, column 6 line 67 bridging column 7 line 23; column 4, line 12-2 1, in particular). The reference TGFb may be administered by intravenous injection (systemic contact), patch, and gels that are slow release (See column 5, line 1-2, column 6, line 45-55, in particular). The US Patent' 825 further teaches a method of diagnosing or testing the presence of active and/or immunological TGFb in female or diagnosing mammals with infertility due to inadequate TGFP (See column 6, line 8-16, column 3, lines 59-65, in particular). The reference method also can be used in conjunction with assisted reproduction such as IVF (See column 3 lines 66 bridging column 4, lines 6, in particular). The US Patent' 825 teaches that TGFb stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular).

The claimed invention in claim 105 differs from the teachings of the reference only in that the method of treating recurrent miscarriage by inducing immune tolerance by exposing mucosal surface of prospective mother with semen or MHC class I antigen of a prospective father capable of eliciting a Th-I response and substantially purified TGFb.

The Specification on overlapping pages 10-11 disclosed that it was well known to one ordinary skill in the art at the time the invention was made that recurrent miscarriage is infertility disease and couple with said problem should be treated together.

Lea et al., teach infertile patients with recurrent spontaneous abortion is deficient in TGFb producing suppressor cells in uterine tissue near the placental attachment site (See abstract, in particular).

Nocera et al., teach human seminal plasma contains both TGFb such as TGFb 1 and TGFb2 and is biologically activated from high molecular weight latent TGFb by acid pH environment of female lower genital tract. Activation of seminal plasma TGFb may immunologically protect the integrity of sperm (See abstract, in particular) and a reduced level of the seminal plasma TGFb may potentially render the spermatozoa immunogenic and lead to the attack by the lymphocytes and other immune cells of the female host (See page 290 paragraph bridging col. 1 and 2, in particular). Nocera et al., further teach TGF-j has been shown to inhibit the generation and killing activity of m-2 activated NK cell (LAK) (See page 283, col. 1, par. 2, in particular).

Clark et al., teach that bioactive TGFS is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Thomas et al teach seminal plasma abrogates the postcoital T cell response to spermatozoal histocompatibility antigens (See abstract, in particular).

Thaler et al., teach seminal plasma regulates maternal immunity for insemination and pregnancy. Seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle (See abstract, in particular).

Prakash et al., teach exposing genital mucosal surface of prospective mother to semen through coitus in the form of ejaculate is a form of immunization. During coitus, the female receives in her reproductive tract (mucosal surface) semen from a genetically dissimilar male. The semen contains immunogenic autoantigens, alloantigens, sperm proteins and seminal plasma adsorbed on sperm surface which are highly immunogenic. However, the female reproductive tract does not appear to be an immunologically privileged site. A potent inhibitor of immune response was indeed found in semen (See page 405, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat recurrent miscarriage, by inducing immune tolerance to a paternal antigen by exposing the female genital mucosal surface of the prospective mother to semen in the form of ejaculate of the prospective father as taught by Prakash et al, Thaler et al and Thomas et al, because recurrent miscarriage is an infertility disease as taught by the known fact disclosed in the Specification on overlapping pages 10-11, along with immunosuppressive factor derived from seminal plaima such as TGFb1 or TGFb2 that suppresses postcoital T cell response as taught by Thomas, prime mothers prior to fertilization for pregnancy acceptance which is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle as taught by Thaler et al, and increasing the success rate of implantation for treatment of infertility such as early embryonic loss, implantation failure, spontaneous abortion and preeclampsia associated with IVF as taught by the US Patent'825.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Lea et al teach infertile patients with recurrent spontaneous abortion is deficient in TGFb2 producing suppressor cells inuterine tissue near the placental attachment site (See abstract, in particular). The US Patent '825 teaches that TGFb stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document.

Clark et al., teach bioactive TGFb is known to suppress the generation of cytotoxic T cells in vitro and has immunosuppressive activity that leads to induction of tolerance in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Nocera et al., teach human seminal plasma contains both TGFb such as TGFb1 and TGFb2 and TGFb1 and TGFb2 are biologically activated from high molecular weight latent TGFb by acid pH environment of female lower genital tract. Thaler et al teach seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamcte intrafallopian transfer treatment cycle (See abstract, in particular).

Claims 107-111 are included in this rejection because the recitation of administering systemically TGFb and one or more antigens or TGFb and one or more antigens each administered at a first site and a different site is an obvious variation of the teaching of US Patent '825 because US Patent' 4825 teaches that TGFb can be administered simultaneously, before or after the antigen and the sites of administration is within the purview of one ordinary skilled in that art at the time the invention was made.

Claim 124 is included because it is an obvious variation of the TGFb since Nocera et al teach human transforming growth factor-p (TGFb) such as TGFb1 and TGFb2 are biologically activated from high molecular weight latent TGFb by acid pH environment of female lower genital tract or plasmin. The recitation of active form is within the teachings of US Patent'825 because administering TGFb and antigens lead to increase the success rate of implantation, which is the active form of TGFb (See entire document, Claims of 825 patent, in particular).

Claim 127 is included because the recitation of multiple exposure and dosing schedule to TGFb and semen or MHC class 1 antigen of the prospective father prior to attempted conception is within the purview of one of ordinary skilled in the art based on the teachings of the Us Patent '825.

Claims 141-144 are included because it is well within the purview of one of ordinary skill in the medicinal art to optimize doses and administration regimen for the particular treatment regimen. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F.2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

In addition, the Examiner disagrees that "one of ordinary skill in the art would have been expected that administering TGF-b to a prospective mother, either before or after attempted conception, would cause miscarriage". It appears that the Examiner and Dr. Clark differ on interpretation of both the claimed methods and the prior art teaching. As is evidenced by Tremellen and by Robertson references there is a different opinion for the role of TGF-b in miscarriage . In the article by Tremellen, it is clearly stated that " semen contains a powerful chemical called TGF-b, which signal the woman's immune system to greet those genetically foreign sperm with open arms rather than xenophobically bared teeth". A team of researchers begin studying whether TGF-b can prevent recurrent miscarriage. Similary, Robertson teaches the therapeutic potential of TGF-b in human miscarriage. Clearly said references indicate that one of ordinary skill in the art would not expect that administering of TGF-b would cause miscarriage.

2. Claims 113 and 114 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 in view of Lea et al (Am J Reprod Immunol (34(1)), Nocera cf al (.Am J. Reprod. Immunology 33: 282-291, 1995) ; Clark et al (Hum Reprod 9(12): 2270-7, Dec 1994,), Thomas et al., (Am J Reprod. Immunol 644): 185-9, Dec 1984;), Thaler et al (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989;) and Prakash et a.,(Reproductive Immunology 70: 403-412, 1981;) in view of the known fact disclosed in the Specification on overlapping pages 10-11 as applied to claims 105-112, 115-125, 127- 132 and 134 above and further in view of Harlow et al., (of record, in A Laboratory Manual, Cold Spring Harbor Laboratory, page 61, 1988',), World Health Organization (of record, in World Health Organization Laboratory Manual for the Examination of Human Semen and Semen Cenical Mucus Interaction, Cambridge University Press, (NY 1987) and Martin-Villa et al (,Biol Reprod 5543): 620-9, Sept 1996,). for the same reasons set forth in the previous Office Action, mailed on 06/20/05 and 03/24/05.

3. Claim 126 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDSI in view of Lea et al (Am J Reprod Immunol 3441): 52-64, July 1995; PTO 892), Nocera cf al (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark et al (of record, Hum Reprod 9412): 2270-7, Dec 1994, PTO 892), Thomas et al (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler et al., (Am J Reprod Immunol 2143-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash et al ., (Reproductive Immunology 70: 403-412, 1981; PTO 892) in view of the known fact disclosed in the Specification on overlapping pages 10-11 as applied to claims 105-112, 115-125, 127- 132 and 134 above and further in view of Grainger et al (Nat Med 149): 932-7, Sep1995; PTO 892) for the same reasons set forth in the previous Office Action, mailed on 06/20/05 and 03/24/05.

4. Claim 133 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDSI in view of Lea et al (Am J Reprod Immunol 3441): 52-64, July 1995; PTO 892), Nocera cf al (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark et al (of record, Hum Reprod 9412): 2270-7, Dec 1994, PTO 892), Thomas et al (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler et al., (Am J Reprod Immunol 2143-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash et al ., (Reproductive Immunology 70: 403-412, 1981; PTO 892) in view of the known fact disclosed in the Specification on overlapping pages 10-11 as applied to claims 105-112, 115-125, 127- 132 and 134 above and further in view of Heidenreich et al., (Am J Reprod Immunol 1994, 3142-3: 69-76,) for the same reasons set forth in the previous Office Action, mailed on 06/20/05 and 03/24/05.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

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